a' cont.

a first subunit comprising a biologically active TGF-β family member fusion protein according to claim 1; and

a second subunit selected from the group consisting of a biologically active TGF-β family member fusion protein according to claim 1 different from that of the first subunit and a wild type TGF-β family protein.

REMARKS

THE CLAIM AMENDMENTS

Applicants have amended claims 10-17 to improve their form.

None of these amendments adds new matter.

THE RESTRICTION REQUIREMENT

The Examiner has required restriction of the claims of this application under 35 U.S.C. § 121 into one of the following thirty six groups:

Group I: Claims 1-5, to the extent that they are drawn to a biologically active TGF-β superfamily member fusion protein comprising a heterologous tissue targeting domain that binds to a cell surface molecule on an osteoprogenitor cell;

Group II: Claims 1-5, to the extent that they are drawn to a biologically active TGF-β superfamily member fusion protein comprising a heterologous tissue targeting domain that binds to a cell surface molecule on a chondrocyte;

Group III: Claims 1-5, to the extent that they are drawn to a biologically active TGF-β superfamily member fusion protein comprising a molecular targeting domain;

Group IV: Claims 1-5, to the extent that they are drawn to a biologically active TGF-β superfamily member fusion protein comprising a heterologous metal binding domain;

Group V: Claims 1-5, to the extent that they are drawn to a biologically active TGF-β superfamily member fusion protein comprising a heterologous protein binding domain;

Group VI: Claims 1-5, to the extent that they are drawn to a biologically active TGF-β superfamily member fusion protein comprising a heterologous ceramic binding domain;

Group VII: Claims 1-5, to the extent that they are drawn to a biologically active TGF-β superfamily member fusion protein comprising a heterologous HAP binding domain;

Group VIII: Claims 1-5, to the extent that they are drawn to a biologically active TGF-β superfamily member fusion protein comprising a heterologous collagen domain;

Group IX: Claim 6-8 to the extent that they are drawn to a latent TGF-β family member comprising a cleavable leader sequence;

Group X: Claim 6-9, to the extent that they are drawn to a latent TGF-β family member comprising a heterologous cleavable leader sequence;

Group XI: Claims 10-16, to the extent that they are drawn to a biologically active TGF-β family member comprising a truncated leader sequence;

Group XII: Claim 17, to the extent that it is drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a TGF-β family member fusion protein different from that of the first subunit;

Group XIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family

member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type TGF-β1 subunit;

Group XIV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type TGF-β2 subunit;

Group XV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type TGF-β3 subunit;

Group XVI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type TGF-β4 subunit;

Group XVII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type TGF-β5 subunit;

Group XVIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type dpp subunit;

Group XIX: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β

family member fusion protein, and a second subunit comprising a wild type Vg-1 subunit;

Group XX: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type Vgr-1 subunit;

Group XXI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type 60A subunit;

Group XXII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type BMP-2A subunit;

Group XXIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type BMP-3 subunit;

Group XXIV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type BMP-4 subunit;

Group XXV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type BMP-5 subunit;

Group XXVI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type BMP-6 subunit;

Group XXVII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type dorsalin subunit;

Group XXVIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type OP-1 subunit;

Group XXIX: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type OP-2 subunit;

Group XXX: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type OP-3 subunit;

Group XXXI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type GDF-1 subunit;

Group XXXII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β

family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type GDF-3 subunit;

Group XXXIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type GDF-9 subunit;

Group XXXIV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type Inhibin α subunit;

Group XXXV*: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type Inhibin βA subunit;

Group XXXVI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF-β family member proteins comprising a first subunit being a TGF-β family member fusion protein, and a second subunit comprising a wild type Inhibin βB subunit; and

Group XXXVII: Claims 19, drawn to a method of purifying a heterodimer of TGF-β family proteins.

The Examiner asserts that the inventions encompassed by Groups I-XXXVII are patentably distinct from one another and have acquired a separate status in the art.

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* The Examiner recited this group as Group XXXIV. Applicant believes that the Examiner intended this group to be XXXV and all subsequent groups to be one number greater than that recited in the Restriction Requirement.

The Examiner states that the inventions encompassed by the following pairwise combinations of products are independent and distinct, wherein neither member of a pair is required for the production or use of the other, and wherein each of the pair can be manufactured independently of the other and used for independent and distinct purposes: Group I and each of Groups II-XXXV; Group II and each of Groups III-XXXV; Group III and each of Groups IV-XXXV; Group IV and each of Groups V-XXXV; Group V and each of Groups VI-XXXV; Group VI and each of Groups VII-XXXV; Group VII and each of Groups VIII-XXXV; Group VIII and each of Groups IX-XXXV; Group IX and each of Groups X-XXXV; Group X and each of Groups XI-XXXV; Group XI and each of Groups XII-XXXV; Group XII and each of Groups XIII-XXXV; Group XIII and each of Groups XIV-XXXV; Group XIV and each of Groups XV-XXXV; Group XV and each of Groups XVI-XXXV; Group XVI and each of Groups XVII-XXXV; Group XVII and each of Groups XVIII-XXXV; Group XVIII and each of Groups XIX-XXXV; Group XIX and each of Groups XX-XXXV; Group XX and each of Groups XXI-XXXV; Group XXI and each of Groups XXII-XXXV; Group XXII and each of Groups XXIII-XXXV; Group XXIII and each of Groups XXIV-XXXV; Group XXIV and each of Groups XXV-XXXV; Group XXV and each of Groups XXVI-XXXV; Group XXVI and each of Groups XXVII-XXXV; Group XXVII and each of Groups XXVIII-XXXV; Group XXVIII and each of Groups XXIX-XXXV; Group XXIX and each of Groups XXX-XXXV; Group XXX and each of Groups XXXI-XXXV; Group XXXI and each of Groups XXXII-XXXV; Group XXXII and each of Groups XXXIII-XXXV; Group XXXIII and each of Groups XXXIV-XXXV; Group XXXIV and Group XXXV. The Examiner further states that

inventions XXXVI and each of I-XXXV are related as process of making and product made*.

Applicants traverse the restriction of Groups I-XXXVII. As discussed during a conference call on November 16, 2001, between Examiner David Romeo, the Examiner's supervisor, Gary Kunz, and applicants attorneys, Karen Mangasarian and Jane Gunnison, applicants believe that the restriction is improperly drawn. During the telephone conference, the Examiner's supervisor, Gary Kunz, recommended that applicants set forth the reasons why the original restriction is improper and request that the Examiner reconsider the restriction requirement based on the discussions during the telephone conference.

The Manual of Patent Examining Procedure (MPEP) states that there are two criteria for a proper requirement of restriction between patentably distinct inventions. The first is that the inventions must be independent or distinct as claimed. The second is that there must be a serious burden on the Examiner if restriction is not required. The MPEP further states that "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to distinct or independent inventions." MPEP § 803.

Applicants request that Groups I-VIII and XI-XXXVI (XI-XXXV based on the Examiner's recitation) be examined together to the extent they relate to any <u>one</u> TGF-β family

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* The Examiner has recited Group XXXIV twice. Applicant believes that each group beyond Group XXXIV recited by the Examiner is intended to be one number greater than that recited. Thus, applicant believes that the Examiner intended to recite 37 groups (i.e.,up to Group XXXVII).

member. If the Examiner agrees to joining these groups, applicants would elect OP-1 as the TGF-β family member for further prosecution in this application. Applicants believe that the proposed combination of Groups does not impose a serious search burden.

The claims of Groups I-VIII are each directed to TGF-β family member fusion proteins comprising a heterologous leader sequence linked to a TGF-β family member protein. The claims of Group XI are directed to TGF-β family member fusion proteins comprising a heterologous leader sequence linked to a TGF-β family member protein, wherein part of the leader sequence is truncated. Thus, a search for a TGF-β family member fusion proteins comprising a heterologous leader sequence linked to a TGF-β family member protein, wherein part of the leader sequence is truncated would necessarily be co-extensive with a search for a TGF-β family member fusion proteins comprising a heterologous leader sequence linked to a TGF-β family member protein.

Furthermore, the claims of Groups XII-XXXVI (XXXV, according to the Examiner's recitation) directed to heterodimers of the TGF-β family member proteins, wherein the first subunit comprises a TGF-β family member protein also should not be separated from the claims of Group I-VIII. The claims of all of Groups I-VIII are directed to TGF-β family member fusion proteins comprising a heterologous leader sequence linked to a TGF-β family member protein. Thus, a search of the fusion proteins of the claims of Groups I-VIII would necessarily be co-extensive with a search of the heterodimer claims of Groups XII-XXXVI. Furthermore, the claims of Groups I-VIII and XI-XXXVI are classified in the same class and subclass (class 530, subclass 350). Therefore, a search of the prior art for Group I, including

both patents and non-patent literature, would be co-extensive with a search of Groups II-VIII and XI-XXXVI and there would be no serious burden for the Examiner to search these groups together.

If the Examiner does not agree with applicants' proposal to rejoin Groups I-VIII and XI-XXXVI, applicants provisionally elect with traverse Group I for initial substantive examination. 37 C.F.R. § 1.143. This election is made expressly without waiver of applicants' rights to continue to prosecute and to obtain claims to the non-elected and/or canceled subject matter either in this application or in other applications claiming priority herefrom.

CONCLUSION

In view of the above, applicants request that the Examiner examine the pending claims in this application. Applicants request favorable consideration and early allowance of the pending claims.

Respectfully submitted,

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I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231 on

December 3, 2001

Claire J. Saintil

Signature of Person Signing

APPENDIX OF AMENDMENTS

10. (Amended) A biologically active TGF-β family member fusion protein [mutant competent to refold under suitable refolding conditions, comprising:] according to claim 1 wherein

[a TGF-β family member protein C-terminal seven cysteine domain, comprising a finger 1 subdomain, a finger 2 subdomain, and a heel subdomain; and

a leader sequence domain operatively linked to said C-terminal domain, whereby] a part [or all] of said leader sequence is truncated.

11. (Amended) The fusion protein [mutant] of claim 10 wherein said truncation is carried out by protease cleavage.

12. (Amended) The fusion protein [mutant] of claim 11 wherein said protease is trypsin.

13. (Amended) The fusion protein [mutant] of claim 10 wherein said truncation is carried out by chemical cleavage.

14. (Amended) The fusion protein [mutant] of claim 13 wherein said chemical cleavage is acid cleavage.

15. (Amended) The fusion protein [mutant] of claim 10 wherein at least one basic amino acid residue of said leader sequence is removed.

16. (Amended) The fusion protein [mutant] of claim 10 [wherein said protein mutant consists] consisting essentially of amino acid sequence SEQ ID NO. 69.

17. (Amended) A biologically active heterodimer of TGF-β family member proteins [,] comprising:

a first subunit comprising a biologically active TGF-β family member fusion protein according to claim 1 [being a TGF-β family member fusion protein]; and

a second subunit selected from the group consisting of a biologically active TGF-β family member fusion protein according to claim 1 [TGF-β family member fusion protein] different from that of the first subunit and a wild type TGF-β family protein.